

Exclusively MRI – Based Molecular Imaging: Can Magnetic Labeling of Physiologically Important Compounds via DNP or Parahydrogen-Induced Hyperpolarization Provide a Potential Supplement or Replacement of PET?

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Abstract: *Molecular Imaging (MI) aims ‘to advance our understanding of biology and medicine through non-invasive in vivo investigations of cellular molecular events involved in normal and pathologic processes’.* – Contemporary molecular imaging concepts combine CT or MRI with PET utilizing ionizing radiation. PET requires cyclotron activation of the isotopes. Desirable especially for children is an exclusively MRI-based MI-method without radioactivity, combining ^1H - and heteronuclear (^{13}C -) MRI using magnetically labeled targets. Though the feasibility has been demonstrated mostly by a Swedish team from the industry, missing is a list of attractive targets and multidisciplinary, less secretive competition in academia without commercial constraints.

The purpose of *Molecular Imaging* has been defined by the Society for Molecular Imaging as ‘to advance our understanding of biology and medicine through non-invasive in vivo investigations of cellular molecular events involved in normal and pathologic processes’. – Today, most molecular imaging concepts – in particular of the brain - combine either Computer Tomography (CT) or MRI with Positron Emission Tomography (PET), e.g. they typically utilize high energy radiation in the form of X-rays or radioactivity. The drawbacks of these powerful methods, however, are the ionizing radiation and the need for activation of the radioactive labels required for PET via a cyclotron. However, especially for the diagnosis and treatment of children, who may only be exposed to one tenth of the dose of radiation permitted for adults, alternate imaging methods, which do not use any kind of ionizing radiation or radioactivity are highly desirable, since then more exposures could be obtained and more frequently, allowing physicians to follow the success of a treatment more precisely.

Accordingly, there is a need (and hence a big interest) in analogous concepts and methods that can provide similar or even identical information at a comparable level of resolution and sensitivity as the above-mentioned combinations. MRI methods by themselves cannot accomplish that at this point, at least not without the help of a signal-enhancement concept.

However, in principle, at least, it is possible to *label various physiologically important compounds magnetically*, for example via generating them *in situ* from appropriate precursors using a hydrogenation employing parahydrogen. The ensuing ParaHydrogen-Induced Polarization (PHIP) generates the required product far from thermal equilibrium, e.g., far from a Boltzmann-type population of its nuclear energy levels of the magnetically active nuclei. The consequence thereof is that such freshly generated molecules give rise to a considerable increase of their magnetic resonance response, which allows their most sensitive detection in MRI systems. Accordingly, magnetically labeled molecules could serve as ‘active’ contrast reagents or magnetic markers, in analogy to radioactively labeled compounds as used in PET.

So far, the feasibility of heteronuclear angiography using PHIP-derived signal enhancement has been demonstrated successfully together with related applications of this concept to other aspects of MRI using hyperpolarized compounds almost exclusively by Swedish scientist, with typically a close industrial affiliation.

Consequently the current status of this field of insufficiently researched or explored field is characterized by two types of shortcomings: On the one hand, there is a lot of secrecy and restriction in the flow of information of what has been done but is still unpublished. Furthermore, what is still missing is a compilation of what is attractive or feasible to be targeted via this technique, because at least in principle, a variety of physiologically active compounds (e.g., amino acids, nutrients, metabolic intermediates, etc.) to investigate metabolism or likewise drugs for treating a variety of diseases including analgesics, antiepileptics, narcotics, neuroleptics etc. could be labeled via hyperpolarizing a variety of magnetic nuclei (^1H , ^2H , ^{13}C , ^{15}N , ^{19}F , etc.) instead of using the radioactive isotopes ^{11}C , ^{13}N , ^{15}O , ^{18}F , etc. allowing selective observation of their distribution, function, and kinetics both in vitro and in vivo. - What about the viable alternative Dynamic Nuclear Polarization (DNP)?

Either way, already targeting and identifying attractive goals and promising systems requires the combined efforts of multidisciplinary teams; therefore, a brain-storming session is most desirable and certainly constructive to boost the interest and potential progress towards developing parahydrogen derived magnetically labeled, i.e., hyperpolarized compounds in combination with either ^1H - or heteronuclear PHIP- enhanced MRI as a potential supplement or alternative to PET. Accordingly, MRI in combination with magnetically labeled compounds would avoid radioactivity, would not require the highly specialized PET scanners of nuclear medicine, but would instead use the rather wide-spread MRI systems, which provide a much higher resolution than PET, albeit at a (still) much lower sensitivity. A multidisciplinary discussion of the various aspects of this complex package of associated problems, of what is desirable or badly needed, and of what seems more realistic or likely to function would certainly have its merits: Among other accomplishments it could help to stimulate a more comprehensive interest in this technique and serve to boost the awareness of both the medical community and of colleagues experienced in the associated physics and chemistry to devote their combined imagination, experiences, and constructive ideas to this challenging potential of PHIP-enhanced MRI, free of commercial interests.

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